Remarks

Claims 1, 2, and 4-6 are currently pending in the application. In order to advance prosecution, Applicants have amended claims 1 and 4-6. A complete listing of all the claims, in compliance with the revised amendment format, is shown above. The amendments to the pending claims are made in order to expedite the issuance of the claims. The amendments are made without prejudice, do not constitute amendments to overcome any prior art rejection, and do not present any new matter.

Priority

The Office Action correctly noted that the instant application claims priority to U.S. Provisional Applications Nos. 60/176,514 and 60/176,515. However, the Office Action accorded a priority date of January 12, 2001, the filing date of the present application. In support of that priority date, the Office Action refers to the reasons set forth in the Office Action of October 27, 2005. However, the claims have been amended since that Office Action and the reasons set forth in that Office Action no longer are applicable. For example, that Office Action argued that "no mention was made of p27, p16 or TGF-beta as a senescence associated, apoptotic or [terminal] differentiation associated marker." However, the present claims no longer are drawn to all markers of senescence, apoptosis, or terminal differentiation, but instead are drawn to specific biological markers. Thus, because the reasons set forth in the Office Action of October 27, 2005 no longer apply to the pending claims, Applicant asserts that the priority date of the invention as presently claimed is January 12, 2000, the filing date of U.S. Provisional Applications Nos. 60/176,514 and 60/176,515, and respectfully requests that Office to accord the present claims with such a priority date.

Discussion of the 35 U.S.C. § 112 Rejection(s)

Claims 1, 2, and 4-6 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The Office Action stated that the final method step does not take into account the cells that were stained by X-Gal and correlation of staining by X-Gal with exposure to the cancer chemotherapeutic agent. Although not acquiescing to this ground of rejection or the Examiner's reasoning supporting the rejection, Applicants have amended claim 1 to recite (emphasis added) ". . . (e) determining whether *X-Gal staining,* expression of the biological marker, *or both X-Gal staining and expression of the biological marker* was increased following exposure to the cancer chemotherapeutic agent." Accordingly, the amended claim includes the features allegedly not accounted for in the final method step. Applicant respectfully contends that this amendment has overcome the asserted ground of rejection.

Discussion of the 35 U.S.C. § 102 Rejection

Claims 1, 2, and 4 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Kopp *et al.* (Cancer Research, 1995, Vol. 55, pp. 4512-4515) ("Kopp"). Applicant respectfully traverses this rejection.

Under 35 U.S.C. § 102, a claim is anticipated only if each and every element as set forth in the claim is found in a single art reference. *Verdegall Bros. v. Union Oil Co.*, 814 F.2d 628, 631 2 U.S.P.Q.2d (BNA) 1051, 1053 (Fed. Cir. 1987); M.P.E.P. § 2131. The identical invention must be shown in complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989); M.P.E.P. § 2131.

The instantly claimed invention is directed towards methods for determining a response to administration of a cancer chemotherapeutic agent to an individual. These methods recite, among other steps, steps for obtaining tissue or cell samples from an individual before and after exposing the individual to a cancer chemotherapeutic agent, staining the tissue or cell samples, and measuring the optical density of the stained tissue or cell samples.

Kopp does not anticipate the present invention because it does not teach or suggest every element as set forth in the claims. Specifically, it does not teach measuring the optical density of stained tissue or cell samples, wherein the stained tissue or cell samples are illuminated with light having a wavelength absorbed by the one or the plurality of stains, as recited by section (d) of amended claim 1. Kopp simply does not teach or suggest staining tissue or cell samples. The Office Action cites Kopp as disclosing a method that includes, among other things, measuring TGF-ß2 in plasma obtained from blood samples. The Office Action even pointed out that collecting a blood sample would fulfill the specific limitation of section (b) of claim 1 regarding collecting a tissue or cell sample from an individual. However, the Office Action failed to recognize that Kopp teaches that it was the protein in the plasma that was stained with the detectably labeled antibody. Therefore, even if collecting a blood sample would fulfill the specific limitation of collecting a cell sample from an individual (which is not admitted), Kopp only teaches measuring TGF-ß2 protein found *in the plasma* of the blood sample. *See, e.g.*, Kopp at 4512, col. 2 ("Plasma TGF-ß2 levels were determined in 20 patients with metastatic breast cancer who received tamoxifen, and in 7 patients with primary tumors without evident metastases who received tamoxifen after surgery in an adjuvant setting."). And, measuring the TGF-ß2 levels found in plasma of an individual does not teach or suggest measuring the optical density even of stained cells (much less stained tissue samples), because plasma is not "cells,"

but rather is the fluid in which cells are suspended. *See, e.g.* Oxford Dictionary of Biochemistry and Molecular Biology, Revised Ed. (2000) at 514 ("plasma: 1. the proteinaceous fluid in which the cells of blood or lymph are suspended, the meaning is sometimes extended to include also the analogous fluid in which the fat droplets of milk are suspended.") (Attached as Appendix A).

Therefore, the practice of Kopp would not accomplish the instantly claimed methods, because it does not teach, among other things, measuring the optical density of the stained tissue or cell samples, wherein the stained tissue or cell samples are illuminated with light having a wavelength absorbed by the one or the multiplicity of stains. Accordingly, Kopp cannot anticipate claims 1, 2, or 4. Applicant, therefore, respectfully requests withdrawal of this rejection and requests reconsideration of the claims.

Discussion of the 35 U.S.C. § 103(a) Rejections

Claims 1 and 4 stand rejected under 35 U.S.C. § 103(a) as being obvious over Park *et al.* (Journal of Cancer Research and Clinical Oncology, 2000, Vol. 126, pp. 455-460) ("Park") in view of Kopp. Applicant respectfully traverses this rejection.

An analysis for obviousness requires a determination of the scope and content of the prior art, the differences between the prior art and the claims at issue must be ascertained, and the level of ordinary skill in the pertinent art must be resolved. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). To establish a prima facie case of obviousness, the Office must show three basic criteria: (1) there must be a suggestion or motivation to combine the reference teachings; (2) there must be a reasonable expectation of success; and (3) all of the claimed limitations must be taught or suggested in the combined prior art references. M.P.E.P. § 2143. The Supreme Court's opinion in the *KSR International Co. v. Teleflex Inc.* case did not alter the basic obviousness inquiry as

established by *Graham*, and, to the contrary, it reaffirmed it. The *KSR* case did reject the rigid application of the "Teaching, Suggestion, and Motivation" test, as applied by the Federal Circuit in that case, but reaffirmed the need to make the analysis explicit when articulating an obviousness rejection based on a combination of the prior art. *See KSR v. Teleflex*, 127 S. Ct. 1727, 1740 (2007), citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.")

The claims as amended recite methods for determining a response to administration of a cancer chemotherapeutic agent to an individual, wherein said method comprises collecting a tissue or cell sample from an individual both before and after exposing the individual to a cancer chemotherapeutic agent, staining both samples with one or a multiplicity of stains that are either X-Gal, a detectably labeled antibody directed against a biological marker or both X-Gal and a detectably labeled antibody directed against a biological marker, wherein said biological marker is p21, p27, p16, or TGF-ß, measuring the optical density of the stained samples, and determining whether X-Gal staining, expression of the biological marker or both was increased following exposure to the cancer chemotherapeutic agent.

None of the cited references, alone or in combination, teach or suggest the instantly claimed method. Park is cited as teaching that the chemotherapeutic agent, hydroxyurea, induces a senescence-like phenotype in human erythroleukemia cells. However, Park only teaches exposing *an isolated, cultured cell line* to a cancer chemotherapeutic agent, hydroxyurea. The amended claims recite tissue or cells samples from *an individual* exposed to a cancer chemotherapeutic agent. This distinction is important, because Park measures a fundamentally

different biological phenomenon than the claimed invention. Specifically, the response to tumor cells in an individual is recognized to be a much more complex interaction than simply treating cancer cells with a drug *in vitro*. This is even truer for immortalized cancer cell lines, such as the K562 cell line used by Park, which have fundamentally different biological properties than even cancer cells found in an individual. In fact, Park only used one cell type, the K562 cell line, in experiments measuring the induction of a senescence-like change. Therefore, rather than using tissue or cell samples obtained from an individual, Park uses an immortalized cell line with anomalous biological properties that are not representative of cells or tissues obtained from a living subject. Accordingly, because Park teaches a fundamentally different method – the exposure of cells to a cancer chemotherapeutic agent *in vitro* – it certainly does not teach or suggest the presently claimed invention that requires that a tissue or cell sample be collected from an individual both before and after the individual is exposed to a cancer chemotherapeutic agent.

The deficiencies of Park are not overcome by the combination with Kopp. Kopp is cited in this ground of rejection as teaching the measurement of TGF-ß2 levels in a patient both before and after chemotherapeutic treatment. However, as explained above, Kopp only teaches measuring TGF-ß2 protein found *in the plasma* of the blood sample. Kopp certainly does not teach staining and measuring the optical density of tissue or cell samples obtained from an individual, much less assessing the response to the administration of a cancer chemotherapeutic agent to such an individual.

Applicant respectfully contends that the Office Action has failed to establish a *prima facie* case of obviousness because first, a skilled artisan would not have been motivated to combine there two references, and second, even if the references were improperly combined, all

of the claim limitations are not even taught or suggested by the combination of Park and Kopp. It is Applicant's position that the obviousness rejection based on this combination of references in the Office Action has been achieved through the use of impermissible hindsight, and that the pending claims are non-obvious over the cited prior art, taken alone or in combination.

For the reasons set forth above, Park and Kopp, taken either alone or in combination, do not disclose the method recited in the amended claims. Accordingly, Applicant respectfully requests withdrawal of this rejection and requests reconsideration of the claims.

Claims 1, 2, 5 and 6 stand rejected under 35 U.S.C. § 103(a) as being obvious over Park and Kopp, and further in view of Bentsen *et al.* (U.S. 6,372,895) ("Bentsen") and Pinkel *et al.* (U.S. 5,665,549) ("Pinkel"). Applicant respectfully traverses this rejection.

The additionally cited references, taken alone or in any combination with the earlier-discussed references, do not teach or suggest the instantly claimed methods. The teaching and deficiencies, as related to the present invention, or Park and Kopp are thoroughly discussed above. The deficiencies of Park and Kopp are not overcome by the combination with Bentsen or Pinkel, either alone or in combination. In this ground of rejection, Bentsen is cited additionally as teaching an image analysis system comprising emission optical filters, collection optics, focusing optics and an optional light guidance system configured to receive multiple emission signals from each fluorogenic enzyme substrate as well as a beam-splitter. Bentsen is also cited as teaching the conjugation of fluorescent labels to antibodies. Pinkel is cited additionally as teaching that an image analysis system can be used to enhance or accurately quantitate the intensity differences relative to background staining differences for more accurate and easier result interpretation.

However, neither Bentsen nor Pinkel teach or suggest that image analysis systems could be used for determining a response to administration of a cancer chemotherapeutic agent to an individual. The Office Action asserts that it would have been obvious "to employ the image analysis system of Bentsen for the detection of fluorescently labeled antibodies witch bind to p21, p16, and p27," and that one "would have been motivated to do so by the teaching of Bentsen regarding the image analysis system for the detection of fluorescently labeled antibodies and the teachings of Pinkel regarding the increased accuracy and ease of interpretation afforded by the image analysis system. However, as set forth in detail above, none of the primary references (Kopp or Park) teach or suggest a method for assessing a response to administration of a cancer chemotherapeutic agent to an individual individually or in combination. Addition of Bentsen or Pinkel, alone or together, does nothing to correct the insufficiencies of the prior references, because Bentsen and Pinkel are only cited for teaching the use of image analysis. Neither Bentsen nor Pinkel teach or suggest any methods that, among other things, involve staining with either X-Gal, a detectably labeled antibody directed against p21, p27, p16, or TGF-ß, or a combination of those stains. In the absence of such teaching, Applicant contends that there was simply no motivation to combine these references. Once again, it is Applicant's position that the obviousness rejection based on this combination of references in the Office Action has been achieved through the use of impermissible hindsight, and that the pending claims are non-obvious over the cited art, taken alone or in combination.

For the reasons set forth above, Kopp, Park, Bentsen, and Pinkel do not disclosure, either individually or in combination, a method for determining a response to administration of a cancer chemotherapeutic agent to an individual. Accordingly, Applicant respectfully requests withdrawal of this rejection and requests reconsideration of the claim.

Conclusion

In view of the above amendments and remarks, the application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue. If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully Submitted,

Date: October 22, 2007

/Andrew W. Williams/
Andrew W. Williams
Reg. No. 48,644

Appendix A

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thought to play a central role in the function of desmosomes and intermediate junctions. Example from human: database PLAK_HUMAN, 743 amino acids (81.40 kDa).

planar 1 of, or pertaining to, a **plane**. 2 lying in one plane; flat.

planchet *or* **planchette** a small, shallow dish used to contain a specimen for determination of its radioactivity with an end-window or windowless counter.

Planck, Max Karl Ernst Ludwig (1858–1947), German physicist; Nobel Laureate in Physics (1918) 'in recognition of the services he rendered to the advancement of Physics by his discovery of energy quanta'.

Planck constant *symbol*: h; a fundamental constant of proportionality between the frequency, ν, of electromagnetic radiation and the energy, E, of a quantum of the radiation; i.e. $h = E/\nu$. It has a value of $6.626\,075\,5(40) \times 10^{-34}$ J s.

plane 1 a surface in which a straight line joining any two contained points lies entirely within the surface; a flat surface. 2 an imaginary surface of such a kind within a real structure or lying conceptually in space. 3 lying wholly in one plane; flat or level; planar.

plane of polarization *or* **plane of polarisation** (of linearly **polarized light** or other electromagnetic radiation) the plane containing the electric vectors of the vibrations.

plane of symmetry a plane through a three-dimensional structure, e.g. a crystal or molecule, that divides the object into two parts that are mirror images of each other.

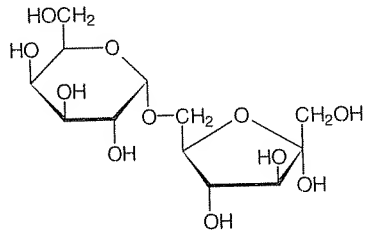
plane-polarized *or* **plane-polarised** *an alternative term for* **linearly polarized**. *See* **polarized light**.

planimeter a mechanical integrating instrument for measuring the area of an irregular plane figure. It consists of a moveable tracing arm, which is made to follow the boundary of the figure, and a dial on which the arm's motion is recorded — **planimetry** *n*.

plankton *the collective term for* the small or microscopic plants (**phytoplankton**) and animals (**zooplankton**), that drift freely in the surface waters of lakes, seas, and oceans.

plant any organism of the kingdom Plantae. Plants are characterized by their ability to effect photosynthesis and the possession of rigid cell walls that contain cellulose.

planteobiose the disaccharide, 6-*O*-α-D-galactopyranosyl-D-fructose; a unit of the trisaccharide **planteose**.



α-anomer

planteose *O*-α-D-galactopyranosyl-(1→6)-*O*-β-D-fructofuranosyl-(2→1)-α-D-glucopyranoside; a trisaccharide isolated from defatted seeds of *Plantago ovata*.

plant hormone *an alternative term for* **phytohormone**.

plantibody a human antibody produced by genetically engineered tobacco plants.

plaque 1 any small disk-like object, patch, or zone. 2 a macroscopic or microscopic rounded clear zone in a layer of cells or bacterial lawn that results from the killing or lysis of adjacent cells by the action of a virus or other agent. 3 **a** (a patch of) fibrous or lipid material on the inner surface of an artery. **b** an area of tissue degeneration with distinctive histological features characteristic of certain (especially neurological) diseases, e.g. **kuru**, **multiple sclerosis**. 4 (a patch of) deposit closely adherent to the surface of a tooth that contains a mixed microbial flora and is composed largely of extracellular bacterial polysaccharide.

plaque-lift a technique used in recombinant DNA technology for screening actively expressing clones. Candidate clones for expression of a particular protein are plated out onto a dish. After incubation a nitrocellulose (or other) membrane is pressed against the surface of the plate, thereby adsorbing any protein 'plaques' formed by actively expressing clones. The membrane can then be screened, and the active clones identified.

+plasia *or* **+plasy** *comb. form* indicating development or growth. —**+plastic** *adj*.

plasm+ *a variant form of* **plasmo+** (before a vowel).

+plasm *comb. form* denoting the colloidal material of which living cells are composed. —**+plasmic** *adj*.

plasma 1 the proteinaceous fluid in which the cells of blood or lymph are suspended; the meaning is sometimes extended to include also the analogous fluid in which the fat droplets of milk are suspended. *See also* **blood plasma**. 2 *a less common word for* **protoplasm**. 3 *(in physics)* any region of highly ionized gas (as in a gas-discharge tube, a hot flame, or a thermonuclear reaction) containing approximately equal numbers of electrons and positively charged ions. It differs from ordinary gas in being a good conductor of electricity and being affected by a magnetic field. —**plasmatic** *or* **plasmic** *adj*.

plasma albumin *an alternative name for* **serum albumin**.

plasma cell *or* **plasmacyte** *or* **plasmocyte** a fully mature antibody-secreting B lymphocyte, found in lymphoid tissue and in connective tissue liable to encounter foreign material. It has an eccentrically placed nucleus, basophilic cytoplasm, and an unusually large amount of rough endoplasmic reticulum.

plasma cholesterol *(in medical biochemistry)* the concentration of cholesterol in blood plasma. In human blood, cholesterol occurs as a component of all plasma lipoproteins, but especially **very-low-density lipoprotein**, **low-density lipoprotein**, and **high-density lipoprotein**. A correlation exists between the level of plasma cholesterol and the occurrence of **atheroma** and heart attacks; this concept is associated with the role of low-density lipoprotein, which has the highest concentration of cholesterol and is thought to be the lipoprotein that distributes cholesterol to the tissues. However, the ratio of high-density lipoprotein cholesterol to low-density lipoprotein cholesterol must be taken into account, as high-density lipoprotein is thought to have a protective function in cycling cholesterol from peripheral tissues back to the liver. The circulating level of cholesterol may be altered by disturbances in carbohydrate and endocrine metabolism (e.g. diabetes or thyroid hormone imbalance), diet, and drugs. It is thought that the level of circulating total cholesterol should desirably be maintained below about 5 mmol L^{-1}.

plasma clearance *see* **clearance** (def. 2).

plasmacyte *an alternative name for* **plasma cell**.

plasmacytoma a tumour of plasma cells; most such tumours secrete myeloma proteins belonging to the same category as monoclonal antibodies.

plasma kallikrein *see* **kallikrein**.

plasmalemma *an alternative term for* **cell membrane**.

plasmalogen any glycerophospholipid in which the glycerol moiety bears an *O*-(1-alkenyl) group at position 1. The term embraces **plasmenic acid**.

plasmalogen synthase EC 2.3.1.25; an enzyme that catalyses the formation of plasmenylcholine from acyl-CoA and 1-*O*-alk-1-enyl-*sn*-glycero-3-phosphocholine with release of CoA.

plasma membrane *an alternative term for* **cell membrane**.

plasmanic acid a derivative of *sn*-glycerol 3-phosphate in which the glycerol moiety is etherified with an alkyl (or alkenyl other than 1-alkenyl) group at position 1 and esterified with an acyl group at position 2; i.e. any 2-acyl-1-*O*-R-*sn*-glycerol 3-phosphate where R = alkyl or *n*-alkenyl when $n > 1$. *Compare* **plasmenic acid**.

plasmanyl *the trivial name for* any phosphoric acyl group de-